

Contains Nonbinding Recommendations

August 18, 2025: Emerging Scientific and Technical Information on Leachable NDBA and Other Small-Molecule Nitrosamines in Infusion Bags

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

1. BACKGROUND

FDA's Center for Drug Evaluation and Research (CDER) has become aware that *N*-nitroso-dibutylamine (NDBA), a small-molecule nitrosamine impurity, has been detected in certain drug products packaged in infusion bags and is concerned about the possibility that NDBA and other small-molecule nitrosamine impurities may leach (migrate) into these products or form from chemicals in printed overwraps or pouches ("leachable nitrosamines"). CDER is currently investigating the root causes and scope of this issue. As described in the CDER guidance for industry, [Control of Nitrosamine Impurities in Human Drugs](#) (September 2024), nitrosamine impurities are of concern to FDA because they are probable or possible human carcinogens. Therefore, we are informing manufacturers and applicants about the issue and providing recommendations for testing and reporting.

Because the data received thus far have been limited, CDER is asking manufacturers and applicants to obtain data to better understand this emerging issue, and applicants to report data in their applications. We anticipate these data will help inform CDER as to the appropriate next steps for addressing leachable nitrosamines in infusion bags.

Drug products packaged in infusion bags are generally used in clinical or hospital settings for acute care; however, there is also use of infusion bags for parenteral nutrition and peritoneal dialysis that may be long-term. While manufacturers and applicants conduct testing and reporting as recommended in Section 4 below, CDER emphasizes that manufacturers and applicants should continue to maintain the development and supply of these products.

Given the unique nature of these products, this context of use, and the source of the impurities, CDER is considering an adjustment factor for the lifetime AI limit, e.g., four- to ten-fold of total nitrosamine exposure, in recommending alternate AI limits for leachable nitrosamines in infusion bags, using the safety risk assessment principles outlined in CDER guidance for industry, [M7\(R2\) Assessment and Control of DNA Reactive \(Mutagenic\) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk](#) (July 2023). Additionally, on a case-by-case basis, applicants may propose higher alternate AI limits than those being considered using this adjustment factor by providing a scientifically justified rationale to FDA. For example, they may seek to do so for large volume products in infusion bags.

2. MAINTAINING THE DRUG SUPPLY WHILE CDER INVESTIGATES SCOPE AND MITIGATION

CDER generally does not intend to object to manufacturers and applicants distributing drug products in infusion bags because the drug products contain leachable nitrosamines while the Agency investigates this issue. As CDER's understanding of the root cause of this issue evolves and potential practices that can remediate or eliminate this concern develop, the Agency may inform application holders of an increase or decrease in the adjustment factor or in the recommended AI limit for these impurities.

Manufacturers and applicants considering an action that is likely to lead to a disruption in the supply of drugs produced at their facilities should contact CDER's Drug Shortage Staff immediately, at drugshortages@fda.hhs.gov. Contacting the Drug Shortage Staff allows manufacturers to meet any obligations to report discontinuances or interruptions in drug manufacture under section 506C of the FD&C Act and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on these products.

3. WHAT IS CURRENTLY KNOWN ABOUT ROOT CAUSES

Thus far, leachable nitrosamines found in drug products packaged in infusion bags appear to be associated with printed overwraps and pouches. Packaging components such as polymeric raw materials, inks, and nitrocellulose in overwraps/pouches may be sources of nitrosamine impurities. Many inks contain dialkylamines, and some inks additionally contain nitrocellulose as binders. Additionally, processes for manufacturing flexible container overwraps/pouches may include heating and compression, which may generate small-molecule nitrosamines.

We are interested in learning whether applicants and manufacturers have identified additional sources of leachable small-molecule nitrosamines and nitrosamine precursors. CDER is also interested in learning more about root causes, effective mitigation strategies, and analytical methods. As investigations proceed and effective solutions are identified, we encourage manufacturers to implement such measures to prevent or reduce the formation of these impurities in drug products. We welcome input from applicants and manufacturers on these issues.

4. TESTING AND REPORTING RECOMMENDATIONS

At this time, CDER is recommending that approved applicants, manufacturers of approved or marketed products, and pending applicants conduct risk assessments on drug products packaged in infusion bags to determine if NDBA and other small-molecule nitrosamines may form from packaging and leach into their drug products. If manufacturers and applicants conclude there is a risk, or if CDER identifies a potential risk, then manufacturers and applicants should test their products to determine the presence of and, if present, the amounts of leachable nitrosamine impurities.

Testing

Testing should be performed on product currently marketed in the U.S. Testing should include at least three (3) representative batches within the labeled expiry, including both distributed and undistributed batches. The strength(s) that may be at greatest risk should be selected.

Testing should be performed using an appropriately sensitive and validated analytical testing method. The limits of quantitation (LOQ) should be scientifically justified based on ICH Q2(R1) principles. (See ICH guidance for industry [Q2\(R1\) Validation of Analytical Procedures: Text and Methodology](#) (November 2005).) CDER recommends methods that are capable of quantifying NDBA and other small-molecule nitrosamine impurities to the parts per billion (ppb) level.

Reporting

As recommended in CDER's guidance for industry, *Control of Nitrosamine Impurities in Human Drugs* (September 2024), the potential risk of nitrosamine impurities leaching from container closure systems, including secondary packaging, should be assessed and if a risk is identified confirmatory testing should be performed. As this is an emerging issue, CDER recommends that applicants share their confirmatory test results to assist CDER. Applicants should report test results and corresponding method validation report as *general correspondence* to their application, with a subject line "Nitrosamine-Related" on the cover letter within 90 days of the publication of this Emerging Scientific and Technical Issues statement. Those applicants and manufacturers unable to submit the test results and method validation report within this 90-day timeframe should submit a *general correspondence* within this same period and provide a detailed plan for conducting the requested testing and validation and the estimated timeline for when you expect to complete the request. Once complete, the results and corresponding method validation report should be submitted as a separate *general correspondence*, again using the subject line "Nitrosamine-Related" on the cover letter.

Manufacturers of marketed products without an application should retain this information and make it available upon request instead of submitting *general correspondence*.

CDER continues to investigate this emerging issue and will provide updates as they become available. If you have questions, you may contact CDER-OPQ-Inquiries@fda.hhs.gov.